



L Please replace the paragraph at page 172, lines 31-37 with the following paragraph: 

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To an aminopropylated glass slide (standard VLSIPS™ Technology) was added a mixture of the following:

 12.2 mg of NVO-Thym-CO<sub>2</sub>H (IX)  
3.4 mg of HOBT (N-hydroxybenzotriazole)  
8.8 µl DIEA (Diisopropylethylamine)  
11.1 mg BOP reagent  
2.5 ml DMF

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Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (pages i - iv).

#### REMARKS

##### Amendments to the Specification

The amendments to the specification correct a number of informalities. The nature of these amendments include correction of typographical, grammatical and spelling errors, correction of priority information and correction of the figure descriptions to correspond with the formal drawings.

##### Information Disclosure Statement

Information Disclosure Statements (IDS's) were filed on April 18, 2001, May 4, 2001, July 12, 2001 and August 3, 2002. Entry of the IDS's is respectfully requested.

##### Substitute Sequence Listing ✓

A Substitute Sequence Listing is being filed concurrently to more correctly describe the artificial sequences of SEQ ID NOS: 1-19. Entry of the Substitute Sequence Listing is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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Dated: 8/14/02

MARKED UP VERSION OF AMENDMENTSSpecification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the first paragraph at page 1 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The present application is a continuation of U.S.S.N. 09/557,875 filed April 24, 2000, which is a continuation of U.S.S.N. 09/056,927 filed April 8, 1998, which is a continuation of U.S.S.N. 08/670,118 filed June 25, 1996, (now U.S. 5,800,992), which is a divisional of U.S.S.N. 08/168,904 filed December 15, 1993, which is a continuation of U.S.S.N. 07/624,114, filed December 6, 1990 (all incorporated by reference), which is a continuation-in-part of commonly assigned patent applications Pirrung *et al.*, U.S.S.N. 07/362,901 (VLSIPS parent) filed on June 7, 1989; and Pirrung *et al.*, U.S.S.N. 07/492,462 (VLSIPS CIP), filed on March 7, 1990 (now U.S. 5,143,854), which are hereby incorporated herein by reference. [The present application] U.S.S.N. 09/577,875, filed April 24, 2000, is also a continuation-in-part of U.S.S.N. 08/348,471 filed November 30, 1994, which is a continuation of U.S.S.N. 07/805,727 filed December 6, 1991 (now U.S. 5,424,186), which is a continuation-in-part of U.S.S.N. 07/624,120, filed December 6, 1990, which is a continuation-in-part of U.S.S.N. 07/492,462, filed March 7, 1990 (now U.S. 5,143,854), which is a continuation-in-part of U.S.S.N. 07/362,901, filed June 7, 1989. Additional commonly assigned applications Barrett *et al.*, U.S.S.N. 07/435,316 (caged biotin parent) filed November 13, 1989; and Barrett *et al.*, U.S.S.N. 07/612,671 (caged biotin CIP), filed November 13, 1990 are also incorporated herein by reference. Additional applications Pirrung *et al.*, U.S.S.N. 07/624,120 (now abandoned) a divisional of which has issued as U.S. 5,744,101 and Dower *et al.*, U.S.S.N. 07/626,730 (now U.S. 5,547,839), which are also commonly assigned and filed on the same day as this application, are also hereby incorporated herein by reference.

Replace the paragraph at page 12, line 12-13 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figs. 4A-4M illustrate [Fig. 4 illustrates] the process of a VLSIPS™ Technology trinucleotide synthesis.

Replace the paragraph at page 18, lines 3-33 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

In the nucleic acid nucleotide sequencing application, a VLSIPS™ Technology substrate is synthesized having positionally defined oligonucleotide probes. See Pirrung et al. (1992) U.S. Pat. No. 5,143,854; and U.S. Patent No. 5,489,678. By use of masking technology and photosensitive synthetic subunits, the VLSIPS™ Technology apparatus allows for the stepwise synthesis of polymers according to a positionally defined matrix pattern. Each oligonucleotide probe will be synthesized at known and [-and] defined positional locations on the substrate. This forms a matrix pattern of known relationship between position and specificity of interaction. The VLSIPS™ Technology allows the production of a very large number of different oligonucleotide probes to be simultaneously and automatically synthesized including numbers in excess of about  $10^2$ ,  $10^3$ ,  $10^4$ ,  $10^5$ ,  $10^6$ , or even more, and at densities of at least about  $10^2/\text{cm}^2$  [ $10^2$ ],  $10^3/\text{cm}^2$ ,  $10^4/\text{cm}^2$ ,  $10^5/\text{cm}^2$  and up to  $10^6/\text{cm}^2$  or more. This application discloses methods for synthesizing polymers on a silicon or other suitably derivatized substrate, methods and chemistry for synthesizing specific types of biological polymers on those substrates, apparatus for scanning and detecting whether interaction has occurred at specific locations on the substrate, and various other technologies related to the use of a high density very large scale immobilized polymer substrate. In particular, sequencing, fingerprinting, and mapping applications are discussed herein in detail, though related technologies are described in [simultaneously filed applications U.S.S.N. 07/624,130, now abandoned] US Pat. No. 5,489,678 and US Pat. No. 5,427,908 [5,427,408], each of which is hereby incorporated herein by reference.

Replace the paragraph at page 87, line 34 through page 88, line 2 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

With a detection method selected, an apparatus for scanning the substrate will be designed. Apparatus[,] as described in U.S.S.N. 07/362,901, from which CIP U.S.S.N. 07/492,462 issued as U.S. Pat. No. 5,143,854[,] , and [or] U.S. Patent No. 5,489,678[,] are particularly appropriate. Design modifications may also be incorporated therein.

Replace the paragraph at page 89, lines 12-28 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The principle of the hybridization sequencing procedure is based, in part, upon the ability to determine overlaps of short segments. The VLSIPS™ Technology provides the ability to generate reagents which will saturate the possible short subsequence recognition possibilities. The principle is most easily illustrated by using a binary sequence, such as a sequence of zeros and ones. Once having illustrated the application to a binary alphabet, the principle may easily be understood to encompass three letter, four letter, five or more[,] letter, and even 20 letter alphabets. A theoretical treatment of analysis of subsequence information, to reconstruction of a target sequence is provided, e.g., in Lysov, Yu., et al. (1988) Doklady Akademi. Nauk. SSR 303:1508-1511; Khrapko K., et al. (1989) FEBS Letters 256:118-122; Pevzner, P. (1989) J. of Biomolecular Structure and Dynamics 7:63-69; and Drmanac, R. et al. (1989) Genomics 4:114-128; each of which is hereby incorporated herein by reference.

Replace the paragraph at page 104, lines 16-31 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Although not described in detail here, but below for oligonucleotide probes, the VLSIPS™ Technology would typically use a photosensitive protective group on an oligonucleotide. Sample oligonucleotides are shown in Figure 1. In particular, the photoprotective group on the nucleotide molecules may be selected from a wide variety of positive light reactive groups preferably including nitro aromatic compounds such aso-nitro- benzyl derivatives or benzylsulfonyl. See, e.g., Gait (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press, Oxford, which is hereby incorporated herein by reference. In a preferred embodiment, 6-nitro-veratryl oxycarbonyl

[oxycarbony] (NVOC), 2-nitrobenzyl oxycarbonyl (NBOC), or  $\alpha,\alpha$ -dimethyl-dimethoxybenzyl oxycarbonyl (DEZ) is used. Photoremovable protective groups are described in, e.g., Patchornik (1970) J. Amer. Chem. Soc. 92:6333- 6335; and Amit et al. (1974) J. Organic Chem. 39:192-196; each of which is hereby incorporated herein by reference.

Replace the paragraph at page 123, lines 7-17 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

With the fingerprinting method as an identification means, problems arise [arises] from mosaicism [problems] in an organism. A mosaic organism is one whose genetic content in different cells is significantly different. Various clonal populations should have similar genetic fingerprints, though different clonal populations may have different genetic contents. See, for example, Suzuki et al. An Introduction to Genetic Analysis (4th Ed.), Freeman and Co., New York, which is hereby incorporated herein by reference. However, this problem should be a relatively rare problem and could be more carefully evaluated with greater experience using the fingerprinting methods.

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